180. (new) The method of claim 139 where the mammal is in need of therapy for combined hypertension and hyperlipidemia.

181. (new) The method of claim 149 where active ingredients (a) and (b) are administered together in a single pharmaceutical composition.

182. (new) The method of claim 145 where the mammal is in need of therapy for combined hypertension and hyperlipidemia.

183. (new) The method of claim 155 where active ingredients (a) and (b) are administered together in a single pharmaceutical composition.

184. (new) The method of claim 151 where the mammal is in need of therapy for combined hypertension and hyperlipidemia. - -

Remarks

Applicants express their sincere appreciation for the interview held on October 24, 2001 involving Examiners Moezie and Jiang on behalf of the PTO and attorneys Rudolf E. Hutz and Robert T. Ronau on behalf of applicants. During the interview, as reflected in the PTO's Interview Summary (PTOL-413), applicants' draft amendment was discussed, especially the proposed new claims, the restriction requirement and status of claims to cardiac risk management, the Warner Lambert trials and the prior art. These matters, as discussed in more detail below, were major subjects of the interview, and applicants thank the Examiners for their careful consideration of the draft in advance of the interview and the helpful discussion of the issues during the meeting with applicants' attorneys. Applicants have amended this application as indicated above and provide the comments and explanations set forth below. Applicants are also submitting an Information Disclosure Statement which, inter alia, again lists certain

references which were lined out and not initialed by the Examiner when submitted earlier. It is respectively requested that the Examiner consider and initial these citations, or indicate why she has not done so.

I. RESTRICTION/ ELECTION

A. Restriction and Election as Applied to Previous Claims

The first Office Action in this application made restriction/election of species requirements based on the original claims. The Examiner found several different Groups of inventions designated as I - VII.

By its responsive amendment, applicants cancelled some claims and added others so that claims 1-3 and 84-172 remained in the case. Applicants also traversed the restriction requirement made in the first Office Action, but elected for further prosecution invention Group VII and the ultimate species of achieving an antihypertensive and an antihyperlipidemic effect in the mammal being treated. By reason of that election, applicants concluded that claims 99-108, 112-114 and 120-144 read on both invention Group VII and the elected species.

Regarding inventions I, VI and VII (the invention Groupings remaining in this application after the prior amendment, and without reference to the elected species), the following claims were present:

Group I	1-3 and 118 (Composition)
Group VI	84-98, 119 and 165-172 (Kit)
Group VII	99-117 and 120-164 (Method)

The Examiner's subsequent April 25, 2001 Office Action modified the invention Groupings of the original restriction requirement by combining Groups I and VI drawn to compositions and kits. However, Group VII was still deemed independent and distinct, and the

restriction requirement as to those Groups I/VI versus VII was made Final. Thus, the respective claims in the two restricted independent and distinct inventions are:

Group I/VI	1-3, 84-98, 118-119 and 165-172
Group VII	99-117 and 120-164

Under these circumstances applicants believe that claims 1-3, 84-98, 118-119 and 165-172 should be withdrawn as directed to compositions and kits (Groups I and VI), which constitute the non-elected invention (the election having been traversed but made FINAL in the last Office Action).

As to the election of species requirement (in the absence of an allowable generic or linking claim), applicants believe that claims 99-108, 112-114 and 120-144 read on the elected species so, within invention VII, claims 109-111, 115-117 and 145-164 should be withdrawn as not reading on the elected species. This in turn should leave claims 99-108, 112-114 and 120-144 as appropriate for action by the Examiner. Should the generic claim (99) be found allowable, then the withdrawn claims should be re-introduced and found allowable.

By contrast, the Examiner has acted only on claims 99-108 and 121-138 (last Office Action, pages 3 and 6), and has withdrawn from consideration claims 1-3 and 84-98 as well as 109-120 and 139-172 (last Office Action, page 3). Applicants respectively submit that claims 112-114 and 139-144 should have been included among the claims acted upon by the Examiner. This is so because, as discussed at the interview, those claims are drawn to the treatment of (preventing or reducing) cardiac risk, and such claims are believed to be sub-generic to the elected species. One skilled in the art will recognize that the treatment of hypertension and/or hyperlipidemia is treatment of cardiac risk because hypertension and hyperlipidemia are each known specific risk factors for cardiac disease. This is reflected at page 4, second full paragraph

of the instant application where applicants stated with respect to hypertension and hyperlipidemia that "both are considered to be major risk factors for developing cardiac disease."

Applicants therefore request that if their broad claims are not allowed in the next Office Action, present claims 112 and 139-144 should be deemed readable on the elected species and therefore acted on.

Furthermore, the Examiner has withdrawn Claim 120 from consideration, but claim 120 is in fact a method claim, which depends on considered claim 99, and it should be acted on as well. At the interview it was agreed that claim 120 had been overlooked by the Examiner.

B. Restriction and Election as Applied to New Claims

By the instant amendment and for the reasons explained below, applicants have deleted certain claims, amended others and added still others. With respect to the claims now pending, applicants believe that the following claims now correspond to invention VII and the elected species.

Group VII 99-101, 106, 109, 112, 115, 120, 132-164 and 173-184
Elected Species 99-101, 106, 112, 120, 132-144 and 173-180

Applicants therefore believe that presently pending claims 99-101, 106, 112, 120, 132-144 and 173-180 should be acted on at this time and respectfully request such action.

II. AMENDMENTS TO THE PRESENT CLAIMS

A. Atorvastatin Clinical Trials By Warner Lambert

Although applicants' attorneys have not yet completed their investigations, they wish to call the Examiner's attention to clinical trials of one component of the claimed mixture. More specifically, before applicants' earliest filing date, Warner-Lambert (then a separate company but now merged into Pfizer) conducted clinical trials to develop data on the safety and effectiveness and for FDA approval of atorvastatin as a lipid-lowering agent (see, for example, the Nawrocki

reference cited by the Examiner). Applicants believe that such pre-filing trials conducted in this country were pursuant to confidentiality agreements with the various participants, but this issue is still being studied.

While the clinical trials were aimed at atorvastatin and its effect on cholesterol levels in humans, it might be assumed that certain of the patients taking part in the trials also suffered from hypertension and thus were already taking amlodipine for this condition before participating in the trials. Needless to say, some patients may not have been hypertensive and may have been taking no hypertension medication. Furthermore, if the patient were taking antihypertension drugs, it might not have been amlodipine.

Alternatively, and subject to the same comments, some patients in the trials may have started to take amlodipine to treat their hypertension while they were already participating in the clinical trial on atorvastatin. Of course, not all patients taking amlodipine during the atorvastatin clinical trial would be relevant to the possible prior art issue here because some of those patients may have received the placebo rather than atorvastatin (in some trials, patients are not provided specific identification of the study drug and patients do not know whether they are receiving an active drug or simply a placebo).

Nonetheless, these clinical trials raise the possibility that, by chance and not by design, patients in the United States were taking amlodipine and atorvastatin, although amlodipine administration and atorvastatin administration were not prescribed by anyone with knowledge of the present invention or by anyone intending to take advantage of the benefits discovered by applicants and described in the instant application. Stated differently, while some patients in the United States may by chance have ingested separate doses of both amlodipine and atorvastatin within a given span of time, this was accidental and not prescribed pursuant to any diagnosis

made by a medical practitioner specifically aware of the advantages of joint administration of the two specific drugs, atorvastatin and amlodipine, practitioner as taught in the present application and seeking to provide those advantages to the patient.

Nonetheless, depending on the outcome of further investigations into the confidentiality obligations surrounding these clinical trials, applicants recognize that a prior art issue may arise respecting these trials. If the trials were conducted in confidence, there should be no issue. If, however, there was no confidentiality as to at least some of the trials and those non-confidential trials included one or more patients who happened to take separately administered and prescribed amlodipine and atorvastatin, certain issues could arise, including whether this chance or accidental occurrence of patients separately prescribed and separately taking amlodipine and atorvastatin (e.g. in different tables, one for each) could be prior art impacting at least some of applicants' prior (or present) claims.

If there is a prior art issue, it would legally fall under considerations applicable to anticipation by inherency. The law is very clear that when dealing with inherency, the burdens are very high to establish that what is claimed was necessarily, inevitably and always practiced in the prior art. In order for prior art to be anticipatory when it is silent as to an asserted inherent characteristic, such a gap must be filled by evidence that the missing descriptive matter is necessarily, inevitably and always present, e.g. Continental Can Co. v. Monsanto Corp., 948 F.2d 1264, 1268-69 (Fed. Cir.1991). It is not sufficient that the prior art event sometimes meets the language set forth in the claims at issue and sometimes does not; it must invariably happen. Glaxo, Inc. v. Novopharm Ltd., 830 F. Supp. 871, 874-77 (E.D.N.C. 1993) aff'd, 52 F. 3d 1043 (Fed.Cir.1995). (Example in prior art which when reproduced sometimes produced the claimed composition and sometimes did not, does not establish inherency.) See also In re Wilding, 535

F.2d 631, 635-36 (CCPA 1976). (Since the starting materials in the prior art reference could be interpreted in two ways, one of which would not show the claimed process, there is no inherency.)

As applied in the instant application, for example, the administration of atorvastatin and chance separate amlodipine administration in these clinical trials was not necessarily, inevitably and always practiced since many patients only received atorvastatin, other patients received a placebo instead of atorvastatin, and the administration of amlodipine to clinical trial patients was purely coincidental. And some patients may have taken no antihypertension drugs while others may have taken antihypertension drugs of a different kind.

Thus, assuming that non-confidential chance and unintended, separate administration of amlodipine and atorvastatin to the same patient were established, it would at best constitute prior art to claims which do not literally distinguish over such chance use. If there is at least one literal difference between what is claimed and the unintended event, then there can be no anticipation (because of those distinctions). Furthermore, the inherent but unintended and unappreciated event cannot be combined with other prior art (or even the skill in the art) to construct an obviousness rejection.

The reason for this limitation on the prior art affect of "inherent" events (i.e. it is anticipation or nothing i.e., it can not be combined with other art in obviousness rejection) is very logical. Obviousness requires, inter alia, a motivation from the art itself to make the changes necessary to move from the art to the invention(s) and that motivation must be coupled with a reasonable expectation of success if the change were made. Both motivation and expectation of success must be separately established. But where the art does not appreciate, intend or recognize a particular event (even though it may have inherently occurred), the event

cannot motivate or teach anything (much less a change needed to reconstruct an invention) and it cannot support any expectation of success.

The case law, and its stated logic, fully support the above statements. Thus, under well-settled Federal Circuit precedent, inherency cannot form the basis for an obviousness challenge to a patent. Kloster Speedsteel AB v. Crucible, Inc. 793 F.2d 1565, 1576 (Fed. Cir. 1986); W.L. Gore & Assocs. v. Garlock, Inc. 721 F2d 1540 (Fed. Cir. 1983) cert. denied, 469 U.S. 851 (1984); In re Spoorman, 363 F.2d 444, 448 (C.C.P.A. 1966)("the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.")

B. The Present Amendments

Applicants desire to move forward with the prosecution of this most important application. They have not completed their investigations into Warner Lambert's clinical trials so they do not know if there really is a "prior art" issue regarding non-confidential, chance and unappreciated separate administration of amlodipine and atorvastatin to a patient in the United States. However, applicants have amended the elected claims so that they literally distinguish over any such chance event, assuming it occurred and it could be considered "inherent" prior art.

All method claims now recite either that amlodipine and atorvastatin are administered together in a single dosage form and/or that administration (whether in single or in separate doses) is pursuant to recognition and with knowledge (and in some instances specific diagnosis and prescription by a medical practitioner) of the benefits of joint treatment with amlodipine and atorvastatin. Clearly, chance events as postulated did not involve any of these affirmatively recited method steps.

Applicants make these amendments without admission or prejudice and solely in an effort to advance the prosecution. They reserve the full right (depending on the outcome of complete investigations) to reintroduce broader claims, perhaps by way of one or more continuing applications.

Thus, per the above amendments, claims 99-101, 106, 109, 112, 115, and 120 are now drawn to elected Group VII (with claims 99-101, 106, 112, and 120) reciting or generic to the elected species) and specify that amlodipine and atorvastatin are administered in combination in a "single pharmaceutical composition". At the interview, it is believed that the examiners appreciated that claims limited to administration of the two specified drugs in a single dose, e.g. tablet or capsule, does distinguish over any possible prior art arising from the Warner Lambert trials for atorvastatin.

Claims 121-126 and new claims 173-174 recite methods for treating a mammal "in need of therapy by the joint administration" of amlodipine and atorvastatin, i.e., at the time of administration, whether sequential, simultaneous or in a single pharmaceutical composition, the patient (e.g. human) was recognized as "in need of joint administration", which means that the benefits of the instant invention were recognized and understood, which of course did not occur respecting the earlier postulated chance events. At the interview, the Examiner agreed to consider such claims but no agreement was reached as allowability over Warner Lambert's trails.

Claims 127-132 and new claims 175-176 are even narrower. They recite methods where the mammal "has been diagnosed as suffering...benefit from therapy by the combined administration...and therefore administration of both...has been prescribed...". These recitations represent even clearer method steps of the recognition of the benefits of the present invention of the patient to benefit, diagnosis and consequent prescription of both drugs for that

treatment benefit. Such methods clearly distinguish over the postulated chance events regardless of whether the two actives are administered in a single pharmaceutical composition or in separate compositions.

Claims 133-138 and new claims 177-178 represent another and narrower variation. They recite methods where combined hypertension and hyperlipidemia are treated in a mammal "which has been examined for both [conditions]...by a medical practitioner and diagnosed as in need of therapy...by joint administration..." of amlodipine and atorvastatin. Thus, as with the earlier claims discussed above, the methods recited in these claims recite inter alia recognition, appreciation, diagnosis and administration, and clearly distinguish over the postulated events regardless how the claimed method is carried out (i.e. in single or separated doses).

Claims 139-144 and new claims 179-180 are counterparts of claims 133-138 and 177-178 but recite the condition as cardiac risk (and thus are sub-generic to the elected species).

Claims 145-150 and new claims 181-182 are counterparts to claims 139-144 and 179-180 but recite the condition as angina.

Claims 151-164 and new claims 183-184 are counterparts to claims 139-144 and 179-180 but recite the condition as atherosclerosis.

III. THE PENDING APPLICATIONS OF DR. R. PRESTON MASON

Applicants direct the Examiner's attention to two applications of Dr. R. Preston Mason which they understand are now pending in the USPTO:

> 09/566,930, filed April 21, 2000 claiming priority to several provisional applications: 60/130,655, filed April 23, 1999; 60/145,305, filed July 23, 1999; 60/151,121, filed August 27, 1999 and 60/166,592, filed November 19, 1999; and
>
> 09/921,479, filed August 3, 2001 claiming priority in provisional application 60/223,214, filed August 4, 2000.

These two pending applications disclose combinations of amlodipine and atorvastatin, and their use in the treatment of various cardiovascular diseases. It is understood that one of these applications has been recently refilled.

Applicants' instant application has an effective filing date of August 29, 1997, which is about twenty (20) months earlier than the first provisional application filed by Dr. Mason. Thus, without addressing to which priority filing date(s) Dr. Mason might be entitled (and for which claims) applicants' present application was effectively filed a little less than two (2) years before Dr. Mason filed his first application.

Because of this significant difference in filing dates, certain publications and activities discussed in applicants' prior amendment constitute statutory bar prior art to Dr. Mason's applications, although they are not statutory bars to applicants' application.

Applicants also advise the Examiner that Dr. Mason and Pfizer Inc. (applicants' assignee) have a relatively recent contractual relationship, which includes an option in favor of Pfizer whereby Pfizer may acquire (at Pfizer's discretion and for payment) all right, title and interest in Dr. Mason's above mentioned applications. At the present time Pfizer has not exercised that option. However, Dr. Mason is cooperating with and conducting research for Pfizer in return for monetary consideration.

By reason of the current contractual relationship between Pfizer and Dr. Mason, the undersigned attorney has received and reviewed documents represented as reflecting the early work by Dr. Mason in connection with the combination of amlodipine and atorvastatin for the treatment of cardiovascular diseases. The undersigned has also reviewed Pfizer's records of its activities in this area. These reviews show the following:

- In April of 1997, Dr. Mason, then a third party researcher (but also a Pfizer consultant), disclosed his concept of an amlodipine/atorvastatin combination and its possible synergism to one of the named applicants and other colleagues at Pfizer. This was substantially after the named applicants had already conceived of the use of amlodipine and atorvastatin in the treatment of heart disease, and Pfizer personnel (including the named applicants) had commenced work towards reducing this concept to practice and initiated steps toward obtaining patent protection.

- As communicated to Pfizer, Dr. Mason's idea embraced both atorvastatin itself and a metabolite of atorvastatin in combination with amlodipine (see Dr. Mason's pending applications for details regarding the metabolite). Prior to applicants' effective filing date for the instant application, Dr. Mason purportedly began actual laboratory experimentation with both atorvastatin itself and its metabolite, alone and in combination with amlodipine. However, the data purportedly generated failed to demonstrate in the test conducted (a study on lipid peroxidation effects) advantages for the combination apparently due to solubility problems with the active ingredients.

- Also, prior to applicants' effective filing date for the instant application, Dr. Mason allegedly tested combinations of atorvastatin metabolite and amlodipine (again in a laboratory antioxidant test). This time the data using the metabolite arguably suggested a benefit for the combination as compared to the individual components alone. Dr. Mason did not then test amlodipine together with atorvastatin, only the atorvastatin metabolite/amlodipine combination.

- Applicants have never specifically disclosed or specifically claimed in their applications any atorvastatin metabolite combination with amlodipine.

- Dr. Mason's next experiments using amlodipine in combination with atorvastatin or its metabolite were many months after applicants' effective filing date and, as stated earlier, Dr. Mason did not file his first application for about 20 months after applicants' date of filing.

Applicants' attorney stands ready to provide further information, explanations and materials respecting Dr. Mason's work if the Examiner so requests.

IV. THE EXAMINER'S PRIOR ART REJECTION

A. Introduction

As the Examiner fully appreciates, applicants' elected claims are directed to certain methods that employ two specific drugs, amlodipine and atorvastatin (or their appropriate salts).[1] Applicants have discovered that of all the many broad classes of drug substances, and the far

[1] For ease of reference, applicants will hereafter refer to "amlodipine" and "atorvastatin" as including both the parent compounds and their pharmaceutically acceptable salts.

greater number of individual drugs within those classes, that have been suggested for use in the field of cardiovascular care, two very specific active chemicals, when used in combination, provide significant benefits in the treatment of the medical conditions recited in the claims.

While each of these two individual drugs was known *per se* for certain medicinal uses, their use together has never been specifically described in the prior art. Thus, applicants' claims have been rejected only as obvious (35 USC §103) and the novelty of the claimed methods is effectively conceded (see page 4 of the Office Action). The Examiner contends, however, that the use of amlodipine together with atorvastatin for the indications claimed is *prima facie* obvious for the reasons set forth in the outstanding Office Action.

While applicants appreciate the thoughtful explanations provided by the Examiner in the Office Action and during the interview, they respectfully traverse this obviousness conclusion and urge reconsideration. When all of the relevant art is taken together as a whole (as it must be in assessing obviousness), there is no teaching or suggestion that these two particular drugs should be selected from the vast array of available compounds, combined and employed in the claimed methods and there is no reasonable expectation of success were that to be done. At best, combinations of various drugs taken from the two broad classes into which amlodipine and atorvastatin fall (amlodipine – an anti-hypertension drug, specifically a calcium channel blocker or "CCB"; atorvastatin- a lipid-lowering HMG-CoA reductase inhibitor) generally have been suggested as an area worthy of scientific investigation, and some specific members of these two classes have actually been combined and evaluated (with mixed and uncertain reported results). By contrast, applicants' claims are very specific, and generalized teachings about combining classes of drugs, and specific combinations of individual drugs (which do not include the specific combination claimed) cannot provide the required suggestion or motivation in the art necessary

to meet the legal standard of *prima facie* obviousness under 35 USC §103. This is particularly true where, as here, the art itself cautions that the effects of these types of combinations are not fully understood or proven, more investigation is needed, and that no conclusions can be drawn. This is the opposite of the teachings needed to establish *prima facie* obviousness.

As emphasized at the interview, the art, taken as a whole, at best places the particular subject matter claimed into a category properly characterized as "obvious to try". But "obvious to try" is insufficient to establish *prima facie* obviousness especially where the claimed combination *per se* is not taught in the art. Hence, the rejection should be withdrawn and applicants respectfully request that action.

B. <u>The Applicable Legal Standards</u>

Applicants believe that the conclusion of *prima facie* obviousness cannot be supported on the present record. The Federal Circuit has frequently explained what must be shown to establish *prima facie* obviousness, and a brief review of the well-established, directly applicable law is essential to understand applicants' position. The specific fact patterns facing the Federal Circuit in the cases discussed below is also instructive in understanding how the legal standards are to be applied.

In re Dembiczak, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999) is a relatively recent case which reversed the Board's holding of obviousness for claims directed to "a large trash bag made of orange plastic decorated with lines and facial features, allowing the bag, when filled with trash or leaves to resemble a Halloween-style pumpkin, or jack-o'-lantern" (at 1615). In reversing the Board's decision, the Federal Circuit explained the analytical framework and burdens necessarily imposed on the Board to establish legal "obviousness" under the applicable statute. The Board had found obviousness based on combining three pieces of prior art— (1) conventional trash

bags in view of (2) "Holiday" (a teacher's handbook describing crepe paper Jack-O'-Lanterns stuffed with newspaper) and (3) "Shapiro" (a paper bag pumpkin stuffed with newspaper, painted orange and having black-painted facial features) (at 1616).

The Federal Circuit explained the law of obviousness as applied to these claims and references in the following manner.[2]

> "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. *** Close adherence to this methodology is especially important in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one 'to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.'" (at 1617)

After extensive citations to authority requiring "strict observance" to the requirement that an Examiner "must identify specifically... the reasons [why] one of ordinary skill in the art would have been motivated to select the references and combine them," the Federal Circuit stated (*Id.*):

> "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight."

Further explaining the required evidence, the Court said (*Id.*):

> "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. *** Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'"

As a basis for reversing the Board, the Federal Circuit held (at 1618):

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[2] The Court supported its discussion of the law by extensive citations to prior decisions which we have omitted from our quotations. Emphasis in all quotations in this Response is supplied by applicants unless indicated to the contrary.

> "Nowhere does the Board particularly identify any suggestion, teaching, or motivation to combine the children's art references (Holiday and Shapiro) with the conventional trash or lawn bag references, nor does the Board make specific—or even inferential—findings concerning the identification of the relevant art, the level of ordinary skill in the art, the nature of the problem to be solved, or any other factual findings that might serve to support a proper obviousness analysis."

The *Dembiczak* decision is not the first, or last, Federal Circuit decision reversing the Board's rejection of claims as obvious in the context of PTO prosecution or addressing the strict requirements and analytical framework essential to assess obviousness. In *In re Geiger*, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987), the Court addressed the Board's rejection of claims to a method of inhibiting scale formation and corrosion of metal using three ingredients each of which had been separately used for this very same purpose. In reversing the Board, the Court noted (at page 1277-78):

> "Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. § 103, to employ these components in combination for their known functions and to optimize the amount of each additive."

Appellant contended that the "PTO has failed to establish a *prima facie* case of obviousness". The Federal Circuit agreed, carefully examined the prior art cited, and found (at 1278):

> "At best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. § 103."

The PTO's failure to establish a *prima facie* case of obviousness (and consequent reversal by the Federal Circuit) was also addressed in *In re Rouoffet*, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998), where the Court noted (at 1455, 1457-58):

> To reject claims in an application under section 103, an examiner must show an unrebutted *prima facie* case of obviousness. *** In the absence of a proper *prima facie* case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent.
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> ***
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> As this court has stated, "virtually all [inventions] are combinations of old elements." *** ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.
>
> ***
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

The CAFC's admonition that combinations of old elements (*i.e.*, elements *per se* taught in the art even for the same purpose as claimed) can still be patentable was restated in *The Gillette Company v. S. C. Johnson & Son, Inc.*, 15 U.S.P.Q.2d 1923 (Fed. Cir. 1990):

> It is true that [the claimed invention] consists of a combination of old elements so arranged as to perform certain related functions. It is immaterial to the issue, however, that all of the elements were old in other contexts. *What must be found obvious to defeat the patent is the claimed combination.*

And the Court carefully distinguished the legal standard of obviousness from "obvious to try"

> [a]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired

> result, or that the claimed result would be obtained if certain directions were pursued. *** However, we have consistently held that "obvious to try" is not to be equated with obviousness under 35 USC 103.

See also *In re Fine*, 5 U.S.P.Q.2d 1596, 1598-9 (Fed. Cir. 1988) (no *prima facie* obviousness; "obvious to try" is "not a legitimate test of patentability"); *In re Jones*, 21 U.S.P.Q. 1941 (Fed. Cir. 1992) (no *prima facie* obviousness even though the prior art generically taught applicants' claimed substituted amine salt of dicamba and the specific salt moiety was known for other acids); *Ecolochem, Inc. v. Southern California Edison Co.*, 56 U.S.P.Q.2d 1065, 1072-3 (Fed. Cir. 2000); *In re Antonie*, 195 U.S.P.Q. 6, 8 (CCPA 1977) and *In re Tomlison*, 150 U.S.P.Q. 623, 626 (CCPA 1966).

C. Taken As A Whole, The Prior Art At Best Merely Makes The Claimed Invention "Obvious To Try"

The proper framework for determining *prima facie* obviousness in this case is to consider all of the relevant art, both that relied on by the Examiner and that cited by applicants in the several Information Disclosure Statements ("IDS") of record in this application.[3] When all of that art is considered, it is clear that the state of the art as of applicants' invention date was uncertain. The data gathered at that point prevented any clear conclusions and merely suggested that further evaluation and testing were needed using drugs from various classes, including those into which applicants' specific combination of amlodipine and atorvastatin fall. These facts, and the absence of any specific suggestions to use the precise combination claimed, mean that there is no *prima facie* obviousness here, only a suggestion or a general proposal "to try" various drugs and combinations of drugs to see what their affects might be.

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[3] See *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988) where the Federal Circuit considered all the prior art, including that cited by the applicant, and reversed the Board's conclusion of obviousness in a reexamination proceeding, holding that, based on all the art, the Board's standard for obvious, "in essence, an 'obvious to experiment' standard ,was improper (at page 1531-32).

The following articles, all identified and submitted in previously filed IDS's, support applicants' position that there is no *prima facie* obviousness, and that this application should be allowed. The first group of articles admittedly are directed to atherosclerosis, a non-elected species. But the Sever article is specifically directed to applicant's elected invention and, especially considered with the other literature, firmly shows that the totality of the art supports only on "obvious to try"

A. The Jukema et al Abstract ("Evidence for... Symptomatic Patients") characterizes lipid lowering therapy as the most effective medical intervention to retard the progression of coronary atherosclerosis, but it also cautions that "The combined effect of lipid lowering therapy and CCB's [calcium channel blockers] has not been reported earlier." To determine whether this combination "might produce a synergistic effect," the authors reviewed data from an earlier REGRESS trial (using pravastatin) and concluded that CCB's act "synergistically with lipid lowering therapy to retard the progression of coronary atherosclerosis". However, in the complete report to which one skilled in the art would refer, Jukema et al concede that the REGRESS trial was "not designed to evaluate combination therapy" (p. 425). The authors (at page 426) indicate that the CCB's involved were nifedipine (32.6%), amlodipine (6.5%), another dihydropyridine (6.7%), diltiazem (49.3%) and verapamil (4.9%). Although an effort was made to differentiate between the various CCB's (dihydropyridines -vs- diltiazem and verapamil) employed in the REGRESS studies, no statistically significant differences could be observed (page 428).

After describing numerous other studies (with somewhat conflicting results and observations – page 429), Jukema et al state, "Whether all CCBs or only some of these drugs are capable of extending the antiatherosclerotic effect of pravastatin is not yet known."

Furthermore, after restating that the REGRESS trial "was not designed to study the effect of CCB administration", the authors concede "no definite conclusions can be drawn concerning the beneficial effect of adding a CCB to lipid-lowering therapy" and that their "results appear to warrant a prospective randomized trial to determine in a more definitive manner the merits of this combination..." (*Id.*).

The data referred to by Jukema et al were generated with pravastatin only, and there is no mention of atorvastatin at all. Moreover, a variety of CCB's were lumped together, only a small percentage of which (6.5%) was amlodipine. Combining these deficiencies with Jukema et al's concession that REGRESS was not designed to study co-administration and that "no definite conclusions can be drawn" (even about pravastatin and CCB's generally), applicants submit that there is nothing in Jukema et al that would motivate one to select a specific CCB (amlodipine – used in only 6.5% of the patients) and a specific statin (atorvastatin – not mentioned at all). At best, this article is an illustration of the art's general recognition that further testing in this broad area was advisable, a classic "obvious to try" and not legal obviousness as required by 35 USC §103.

B. Orekhov et al ("Anti-atherogenic Effect of Calcium Antagonist Plus Statin Combination") also describe the REGRESS trial where lipid-lowering therapy with pravastatin in combination with calcium antagonists was said to be more effective than a statin alone. The authors attempted to elucidate the mechanism of the combination on atherosclerotic lesions using amlodipine and lovastatin in a described *in vitro* test (p. 350). The findings "may serve as an explanation" of the "more pronounced anti atherogenic effect at the lipoprotein level of amlodipine-lovastatin co-treatment compared with amlodipine alone (*Id.*). The co-treatment here was with lovastatin, and atorvastatin is not mentioned.

C. Other studies specifically directed to the effects of either CCB's *per se* or lipid-lowering agents *per se* (*i.e.*, the "study drug") have enrolled patients who already were taking another drug, but no analysis seems to have been made to ascertain whether such a chance event (the study drug given to patients already taking another drug) provided any benefit. Thus see Lichtlen *et al* ("Retardation of... Nifedipine" – The Lancet, Vol. 335, pp. 1109-13, 19909) where the test was intended to assess the effect of nifedipine (a CCB) but other drugs taken at study entry by some patients included oral nitrates (46% in nifedipine group), beta blockers (39%), antiplatelet agents (38%), anticoagulants (16%) and lipid-lowering drugs (6%); these additional medications did not change substantially throughout the study (page 1110). Another relevant article is Waters *et al* ("Progression of Coronary Atherosclerosis" – Circulation, Vol. 82, No. 6, Dec. 1990, pages 1940-1953), where at pages 1941 and 1947 subjects administered nicardipine (the study drug, a CCB) also took medications such as β-blockers, long-acting nitrate, aspirin, digitalis, diuretics and/or oral hypoglycemic agents.[4]

D. Kramsch and Sharma ("Limits of ... Anti-atherosclerotic Agent" – Journal of Human Hypertension (1995) 9 (Suppl. 1), S3-S9) discuss treatment of atherosclerosis by decreasing low-density lipoprotein cholesterol (LDL-C). After observing that recent trials revealed that atherosclerosis progression was arrested in only 50-60% of patients, the authors state, "it is clear that lipid-lowering therapy has limited efficacy and there is therefore a need for other drugs" (p.

[4] At page 1951, the authors state under "Implications", "The possibility that calcium channel blockers might act synergistically with cholesterol lowering to induce regression and retard progression should be considered, particularly for early lesions," again a broad suggestion for further study and an expression of uncertainty as to the ultimate result. This cannot be considered as a motivation or even reasonable expectation of success for a specific mixture of amlodipine and atorvastatin, two drugs unmentioned by Waters *et al*.

S3, Summary).[5] To "test this hypothesis", a new calcium antagonist, amlodipine, was studied in non-human primates for its anti-atherogenicity.[6] Those results "suggest that amlodipine may be an excellent candidate, in combination with lipid-lowering drugs, for dual therapy of atherosclerotic vascular disease and may also be effective as monotherapy even when LDL-C is not lowered satisfactorily (*Id.*)." At page S7, the Kramsch article says "the data indicate that amlodipine may be effective...".

Note that Kramsch et al do not mention atorvastatin and that the data only "suggest" or "indicate" that dual therapy "may" be of benefit. At best, these teachings are speculative on their face and again present a classic "obvious to try" hypothesis, not obviousness under 35 USC §103.

As mentioned earlier, the above literature primarily addresses atherosclerosis treatment, which the Examiner has considered separate and distinct from the elected species. However, the Sever article cited and relied on by the Examiner is believed to "fill the gap" and to establish that the same uncertainty exists as to the treatments of the elected invention. More specifically, Sever is directed to "The hypertension trials" (emphasis supplied). It discusses anti – hypertensive treatment.

After reviewing the findings of several trials, Sever addresses "What the trials have failed to tell us" (page S-30) and explains that one reason for the "shortfall" of the trials is "Failure to recognize other risk factors", including cholesterol levels (page S-31 first paragraph).

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[5] The authors refer to several trials including CLAS (niacin and colestipol), MARS (lovastatin), FATS and POSCH (the latter two study drugs are unspecified). See pages S3-S4.

[6] Other calcium antagonists mentioned are nisoldipine, lacidipine, nifedipine, nicardipine, isradipine, verapamil and diltiazem (p. 57).

Thus Sever ("The Hypertension Trials" – Journal of Hypertension 1996, Vol. 14 (Suppl. 2), pp. S29-S34), a reference specifically relied on by the Examiner in the rejection of record, after discussing numerous prior clinical trials aimed at the effects of various antihypertensive treatments (page S 32, Tables 2 and 3), admits to the "Need for further studies" (p. S31). After referencing the "uncertain" impact of newer drugs, Sever states:

> "Clearly, there is a need for further trials to define the effects of these newer agents [α-blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists] and to answer some of the remaining issues. Among the questions that remain today are... (3) what are the benefits of treatment in patients with coexisting disease or risk factors, including dyslipidaemia, diabetes, coronary heart disease, stroke, left ventricular hypertrophy, etc.? (4) what are the benefits of combining lipid-lowering, aspirin or antioxidant therapy with antihypertensive therapy in hypertensive patients."

Thus Sever, in 1996, with full knowledge of these studies, including the very portion pointed to by the Examiner, finds unanswered questions and the need for "further trials". This is the hallmark of "obvious to try" and not obviousness under 35 USC § 103.

While other articles and patents among those presented in applicants' several IDS's also are relevant to the *prima facie* obviousness issue, the above citations are believed to demonstrate the uncertain nature of the art at about the time of applicants' invention date and the mere invitation to experiment further, without any clear teaching of success. This is a classic "obvious to try" various combinations and permutations of cardiovascular-treatment agents and not the motivation and direction specifically to combine two precisely stated drugs as claimed, much less any reasonable expectation of success.

D. The Examiner's References and Rejections

The Examiner has cited three references to support the conclusion of *prima facie* obviousness reached in the Office Action. Their teachings, and deficiencies, are as follows:

Messerli addresses a controversy that arose in 1995 about CCB's which cast temporary doubts by some on calcium antagonists used to treat hypertension. The article criticized "recent publications" which purported to show increases in the rate of heart attack and mortality, and discussed more recent studies including those using amlodipine, nifedipine, felodipine, nicardipine and diltiazem. Messerlli concluded (p. 1805) that "Until the results of the above ongoing prospective studies are available, we should be highly critical of retrospective case control studies, deceptive meta analyses, and other bouillabaisse." At best, Messerli teaches that amlodipine is a recognized and useful treatment for hypertension, a fact freely acknowledged by applicants. But it teaches nothing about any combination of amlodipine and a statin lipid-lowering agent, especially atorvastatin, which is not mentioned anyplace in the Messerli article. In fact, the article does not address combination therapy at all.

Nawrocki teaches atorvastatin as a promising treatment for hypercholesterolemia. It is a member of the class of lipid-lowering or lipid-modifying drugs called HMG-CoA reductase inhibitors. While teaching atorvastatin for this treatment, the Nawrocki article does not mention anti-hypertension drugs, much less CCB's, much less the specific CCB, amlodipine, and it does not address combination drugs of any kind.

At page 5 of the Office Action, the Examiner states as a general proposition that it would have been obvious "to combine the known active agents useful in the same method into a single composition for the same purpose." Applicants disagree. By pinpointing amlodipine and atorvastatin, from among the many, many individual species of known drugs useful to treat

cardiovascular disease and particularly hypertension and hyperlipidemia, the Examiner has already used hindsight and applicants' own disclosure as a blueprint for selecting references and reconstructing the invention. What in the totality of the art leads one to select and concentrate on these two specific members of the broad drug classes involved? And, what in these two references suggests combination therapy of any kind, much less the use of these two specific agents from among all the other available species of drugs in the relevant classes? Applicants submit there are no such teachings and that the rejection must fail as it did in *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994) where the Federal Circuit reversed the Board concluding that the fact that the claimed subject matter may be encompassed by the generic teachings of the prior art, there was nothing in the art that suggested that one should select the necessary variables needed to reconstruct what applicant was claiming.

Moreover, the Examiner's reference to the obviousness to "combine the known active agents useful in the same method into a single composition for the same purpose" is a legally incorrect application of the law of obviousness. It was specifically rejected by the Federal Circuit in *In re Geiger* (*supra* page 16) where a rejection based on this same theory was reversed with the Court's comment:

> "Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. § 103, to employ these components in combination for their known functions and to optimize the amount of each additive."
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> At best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. § 103.

The Examiner also points to Sever as providing "motivation" for the claimed method (page 5 of the Office Action). The Examiner contends that Sever teaches that "combining antihypertensive therapy with lipid-lowering drugs would be beneficial," citing to pages S32 2d paragraph of left column and page S33, the last paragraph of left column (Office Action, page 4). The second paragraph, left column of page S-32 actually says that combinations of drugs "need to be evaluated," and page 33 references. "Further trials [that] are currently being planned or are in progress" and not results, much less a specific combination as claimed for the treatment claimed.

Additionally, as discussed in Section III, E above and notwithstanding the Examiner's contentions about motivation, Sever says nothing more than "further trials are currently being planned or are in progress" to evaluate the effects of various drug combinations (p S33). More importantly, and despite the admitted facts that amlodipine and atorvastatin were each known alone, Sever never teaches a combination of atorvastatin and amlodipine, two specific members among the numerous combinations and permutations of possible active agents mentioned in the article. At best, Sever's teachings make it "obvious to try" any one of a significant number of possible drugs and drug combinations and says more tests. are needed even for general conclusions. But obvious to try is not the legal standard of obviousness under 35 USC §103, and, far from teaching any reasonable likelihood of success, Sever merely poses the questions "What are the benefits...?" (page S31).

There is simply no teaching in the art which raises a *prima facie* case of obviousness leading to the specific and very limited combination claimed. Applicants respectfully urge that the obviousness rejection be withdrawn. The obviousness rejection as proposed by the Examiner can not be sustained based on a general proposition that each drug is known per se or even that

There is simply no teaching in the art which raises a *prima facie* case of obviousness leading to the specific and very limited combination claimed. Applicants respectfully urge that the obviousness rejection be withdrawn. The obviousness rejection as proposed by the Examiner can not be sustained based on a general proposition that each drug is known per se or even that one or both were known to be particularly effective. In light of Sever, and the other teachings of uncertainty, need to test, etc as to general combinations of drug classes, there is nothing to motivate selection of these two specific drugs for use as claimed or any reasonable expectation of success.

V. THE DOUBLE PATENTING REJECTION

Because this is a provisional obviousness-type double patenting rejection, applicants request that the rejection be held in abeyance pending allowance of subject matter in one or more of applicants' relevant applications. At this point, applicants note, however, that they respectfully disagree with the contention that there truly is double patenting involved.

A prompt and favorable response is earnestly solicited. If the Examiner believes that further discussion, face-to-face or by telephone, would advance the prosecution, please contact the undersigned.

Respectfully submitted,
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Dated: October 25, 2001

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